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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/819,669
Filing Date: March 17, 1997
Appellant(s): BOON ET AL.

Norman Hanson
For Appellant

SUPPLMENTAL EXAMINER'S ANSWER

This Supplement Examiner's Answer is in response to the Reply Brief filed 11/16/04.

I. Grouping of Claims

Appellant asserts that the examiner has exceeded his authority and has taken claims 189-191 and placed them in a third Group.

Appellant asserts that there is no provision for this type of action on the examiner's part.

According to MPEP 1208, page 1200-18, the Examiner's Answer must state:

"Whether the Examiner disagrees with any statement in the Brief that certain claims do not stand or fall together, and, if the Examiner disagrees, an explanation as to why those claims are not separately patentable."

With respect to appellant's assertions that the examiner has exceeded his authority, setting forth an additional Group was based upon an explanation on why there was a disagreement with the Grouping of Claims set forth by appellant, which is consistent with MPEP 1208.

However, irrespective of appellant's opinions concerning the examiner's authority, it is noted that appellant has agreed to the Grouping of Claims 189-191 together, as a separate Group.

In response to appellant's inquiry, the examiner did not apply the reference (k) the Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994 in the prosecution of the instant application prior to the Examiner's Answer.

As pointed out in Section (7) Grouping of Claims of the Examiner's Answer as follows:

"Appellant's statement in the Brief that certain claims do not stand or fall together is not agreed with because a third group drawn to "in the form of a vaccine" recited in claims 189-191 should be included as a third Grouping of the claims. Given that a vaccine must by definition provide an immunoprotective response upon administration, claims drawn to a "form of a vaccine" should be considered separately.

"The following definition of a vaccine is found on page 309 of the Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994."

"Vaccine: Live attenuated or killed organisms or parts or products from them which contain antigens that can stimulate a specific immune response consisting of protective antibodies and T cell immunity. A vaccine should stimulate a sufficient number of memory T and B lymphocytes to yield effector T cells and antibody-producing B cells from memory cells. It should also be able to stimulate high titers of neutralizing antibodies. Invention of a vaccine into a nonimmune subject induces active immunity against the modified pathogens."

Although the examiner maintains that the rejections under 35 USC 112, first paragraph, written description and enablement should be maintained over all of the claims / Groups, it is acknowledged that the claimed limitations of Groups II and III can be considered apart from the broader generic claims of Group I."

Dictionaries are one source for determining the ordinary meaning of a claim term. See Texas Digital Sys. v. Telegenix, Inc., 64 USPQ2d 1812 (Fed. Cir. 2002).

In contrast to the rejections based upon the claimed recitation of "vaccine", it is noted that the rejections under 35 USC 112, first paragraph, written description and enablement, have relied, in part, upon the following, which was first employed in the Office Action (see pages 4, 9 and 10), mailed 3/2/04, and reiterated in the Examiner's Answer (see pages 13-15 and 22-24 as well as Response to Arguments).

Even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al., APMIS 106: 665-679, 1998).

In discussing the structure and expression of MAGE family genes, De Plaen et al. (Immunogenetics 40: 360-369, 1994) note: "Throughout the MAGE family ..., there is considerable conservation of hydrophilic and hydrophobic regions, suggesting that the proteins produced by all these genes may exert very similar function. At the present time, however, there is no indication regarding this function." (see page 367, column 2, paragraph 2).

It is noted that the MAGE genes do not seem to be expressed in normal tissues except testis and placenta (see De Plaen et al., page 368, column 1, paragraph 2). While the MAGE genes may have the potential to code for antigens that could be targets for specific anti-tumor T lymphocyte responses, such responses would rely upon various regions of the different MAGE proteins contributing peptides that combine with various HLA class I molecules (page 368, column 1, paragraph 2).

The reliance upon the function of the claimed tumor rejection antigen precursors depends, in part, upon the antigen processing and presentation of MAGE-derived peptides, which, in turn, can form targets for cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Although appellant has argued and distinguished between different classes of tumor or tumor-associated antigens (e.g. tum and TSTA) in defining the MAGE family encompassed by the claimed invention, the following of record was provided to show that defining human tumor antigens, including human tumor antigens that result to stimulating cytotoxic T lymphocytes to tumors was difficult at the time the invention was made.

Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan. For example, Stevenson (FASEB J 5: 2250-2257, 1991) reviews tumor vaccines and tumor antigens (see entire document) and notes the following. "The first problem in discussing tumor antigens is one of nomenclature. The original definition of a tumor-specific transplantation antigen (TSTA) was an operational one based on the ability of a sensitizing dose of a particular tumor given to syngeneic animals to elicit T cell-mediated rejection of a subsequent challenge of those tumor cells" (see page 2251, column 1, paragraph 1 of Tumor Antigens). "Attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty" (page 2251, column 2, paragraph 2).

Therefore, rejections based upon the lack of immunogenicity to induce immune response in vivo as properties of tumor antigens and tumor vaccines (see claims 189-191) comprising MAGE tumor rejection antigen precursor proteins were elements of the rejections of record.

Appellant distinguished Groups between the claimed limitations based upon a recitation of a particular tumor rejection antigen peptide, namely SEQ ID NO: 26.

In turn, the examiner distinguished a third Group based upon the recitation of "vaccine" as a claimed characteristic of the claimed subgenus of "compositions comprising MAGE tumor antigens in the form of a vaccine" (see claims 189-191).

Given appellant's assertions that the claimed MAGE tumor rejection antigen precursor proteins are supported by isolation and characterization of all of the disclosed MAGEs which satisfy the *TRAP characteristics (i) – (iv)*
and given the absence of a definition of vaccine in the specification as filed, the examiner introduced a dictionary definition into the record for clarity.

The Dictionary definition is consistent with the plain and ordinary meaning attributed to the word "vaccine" by persons skilled in the relevant art and that with the specification as filed at the time the invention was made.

As described on page 55, paragraph 1 of the instant specification, the disclosure make clear that the sequences code for **tumor rejection antigen precursors (TRAPS** which, in turn are processed into **tumor rejection antigens (TRAs)**. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. TRAPS which are processed into TRAs and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions as vaccines.

Appellant does not appear to dispute the submitted dictionary definition of "vaccine".

II. Art of Record

In contrast to appellant's assertion that the examiner listed the references as "PRIOR ART", it is noted that Section (9) Art of Record of the Examiner's Answer indicates "Art of Record", not "Prior Art".

While it is acknowledged that the Art of Record lists post-filing date references, appellant is reminded that there is no bar to reliance on post-filing date references, if appropriate.

It is acknowledged that Ding et al., Biochem. Biophys. Commun. 202: 549-555, 1994 (Reference F) was not cited in the rejections set forth in the Examiner's Answer.

This was not an oversight by the examiner. Rather, the reliance upon Ding et al. was not deemed necessary to support the rejections of record, particularly given the number of references already relied upon in the rejections of record.

Further, it was the examiner's intention to focus the evidence provided by the co-inventors in the instant application and in De Plaen et al. (Immunogenetics 40: 360-369, 1994) (Reference E in the Examiner's Answer) to address the basic information concerning the structure and expression of the genes of the MAGE family.

Such evidence was deemed important in contrasting appellant's assertions that the instant specification does provide for 11 species that meet the key *TRAP characteristics (i)-(iv)* of MAGE, including:

(i) they are proteins that are encoded by naturally occurring, non-mutagenized gene;

(ii) they are characteristic of cancer cells and are not expressed by normal cells (with the exception of testes cells;

(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions; and

(iv) they are processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs.

with the evidence itself, particularly with the evidence generated by appellant, concerning the structure, expression and function of the disclosed MAGEs.

With respect to written description,
Adequate written description require a precise definition, such as structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. Appellant has not satisfied the written description of the MAGE TRAP genus of polypeptides in the absence of a disclosed correlation to a structure and possessed a sufficient number of species that satisfy the *MAGE TRAP protein characteristics (i) – (iv),* as asserted by appellant.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 itself, much less, nucleic acids hybridizing to SEQ ID NO: 8, and any or all of the *TRAP properties / characteristics (i)-(iv)* outlined above.

With respect to enablement,
The teachings in the specification provide for a plan or an invitation to the skilled artisan to experiment practicing the claimed but do not provide sufficient guidance and specificity how to apply detailed, relevant identifying characteristics in making and using MAGE TRAP proteins that satisfy the *TRAP characteristics (i)-(iv)* in order to execute that plan.

In support of the unpredictability of the claimed genus of MAGE TRAP proteins, the evidence supports the contention that strategies drawn to isolating and determining a MAGE TRAP protein that satisfies the TRAP characteristics (iv)-(iv) have not universally straightforward or as easy to apply as was initially disclosed in the specification as-filed nor has the interpretation of results always been unambiguous.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, appellant does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species, not all of which meet the critical *characteristics of MAGE TRAPs* asserted in the Brief and the Reply Brief.

III. REPLY TO THE EXAMINER'S ANSWER WITH RESPECT TO THE WRITTEN DESCRIPTION REJECTION

As appellant notes that the features of the claimed invention have been discussed in appellant's Brief of record; so too, the examiner has addressed the features of the claimed invention in the Examiner's Answer of record.

Appellant then notes that:
"MAGE-5 is presented as SEQ ID NO: 16. It is labeled as genomic DNA, but within nucleotides 645-908, one finds the sequence presented in triplets, i.e. a coding region. One of ordinary skill in the art recognizes such as the molecule that constitutes cDNA, because cDNA contains only coding regions."

In addition, appellant also indicates that this is true for MAGE-51 (presumably MAGE-5), 6, 7, 8, 9, 10 and 11.

First of all with respect to appellant's last line on page 3 of the Reply Brief,
"One of ordinary skill in the art recognizes such as the molecule constitutes cDNA, because cDNA contains only coding regions",
the following is noted.

This statement appears to be misleading in that complementary DNA (cDNA) is not limited to coding regions, but cDNA can contain both coding and non-coding nucleic acids.
Here in the present case, it appears that appellant does acknowledge that genomic DNA, not cDNA was disclosed in the application as filed.
Further, appellant appears to acknowledge that all of the coding regions of the disclosed MAGE genomic DNAs do not each encode an entire MAGE tumor rejection antigen precursor protein, as encompassed by the instant claims.

Back with respect to appellant's reliance on MAGE-5, it is noted that co-inventors co-authored paper De Plaen et al. (Immunogenetics 40: 360-369, 1994) (listed as (E) in the Art of Record in the Examiner's Answer) describes the following concerning MAGE-5.

As pointed out in the evidence addressed and provided in the Examiner's Answer,

The structure of genes MAGE 5 and 7-11 has not yet been completely defined because no cDNA clones have been obtained up to now.
See page 364, column 2, paragraph 1 of De Plaen et al. Immunogenetics 40: 360-369, 1994 (Reference E of the Examiner's Answer).
Also, see page 8 of the Examiner's Answer, for example.

MAGE-5, 8, 9 10 and 11 were very weakly expressed in all the samples that we examiner; we estimated that the amount of RNA of these genes represented less than 1% of that of the highly expressed genes. We were unable to retrieve in a MZ2-MEL library a single cDNA corresponding to MAGE-5, suggesting the presence of <2 copies/cell.
MAGE-7 was not transcribed at all in the 95 tumor samples.
See page 367, column 1, paragraph 2 of De Plaen et al.
Also, see page 8 and page 30, paragraph 8 of the Examiner's Answer, for example.

Most of the putative MAGE proteins are 309-319 amino acids long.
See page 365, column 1, paragraph 1 of De Plaen et al. Immunogenetics 40: 360-369, 1994.
Also, see page 8 of the Examiner's Answer, for example.

In contrast to describing adequate written description and to enabling how to make and use MAGE tumor rejection antigen precursors that satisfy the *TRAP characteristics (i)-(iv)* asserted by appellant,

not all of the sequences presented in triplets for MAGE-5 (SEQ ID NO: 17), MAGE-6 (SEQ ID NO: 16), MAGE-7 (SEQ ID NO: 19), MAGE-8 (SEQ ID NO: 20), MAGE-9 (SEQ ID NO: 21), MAGE-10 (SEQ ID NO: 22) and MAGE-11 (SEQ ID NO: 23) can account for encoding the entire size of 309-319 amino acids of putative MAGE proteins nor for satisfying the *MAGE TRAP characteristics (i)-(iv)*.

For example in the case of MAGE-5, nucleotides 645-908 equals 263 nucleotides divided by 3 (triplet, codon) equals 87.6 amino acids, which does not account for a putative MAGE proteins of approximately 309-315 amino acids long.

As Example 31 on pages 48-49 of the instant specification as filed discloses, the MAGE-5 that was determined by homology appears to be a "fragment" and not full-length.

Again, it does not appear that MAGE-5, 7, 8, 9, 10 and 11 are expressed by tumor cells.
For example, see Table 2 on page 367 of De Plaen et al. Immunogenetics 40: 360-369, 1994, as well as Example 36 on pages 51-52 of the instant specification.

In contrast to appellant's assertions, the rejections of record are not based solely on the issue that MAGE-7 was not found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes.
See page 365, column1, paragraph 1 of DePlaen et al. Immunogenetics 40: 360-369, 1994.
Also, see page 8 of the Examiner's Answer, for example.

Appellant is invited to the time to review the detailed analysis of the Examiner's Answer with respect to the facts and issues concerning the rejections under 35 USC 112, first paragraph, written description and enablement, and how these 112, first paragraph, issues are addressed in the context of the *MAGE TRAP characteristics* (i)-(iv), which appellant has applied in defining the claimed MAGE tumor rejection antigen precursor proteins.

Again, appellant asserts that homologous nucleotide sequences can be expected to encode homologous proteins, which in turn, behave homologously.

Further, appellant submits that a nucleic acid molecule which differs form SEQ ID NO: 8 by one nucleotide would hybridize to it and that such nucleic acid molecules are TRAPs.

As noted previously, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (Trends in Biotech. 18:34-39, 2000) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36).

Similarly, Bork (Genome Research 10:398-400, 2000) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399).

Smith et al. (Nature Biotechnology 15:1222-1223, 1997) remark that there are numerous cases in which proteins having very different functions

While appellant has argued previously that the instant disclosure is not relying upon sequence databases, appellant's reliance upon hybridizing language with genomic DNA is subject to the same or similar issues concerning reliance upon sequence homology in databases in that appellant clearly states that homologous proteins behave homologously. Whether the homology or sequence identity between different sequences is achieved via comparing databases or via hybridization conditions, the issues of the relationship between the disclosure of a limited number of species and broad claim coverage is based similarly on the relationship or correlation of structure to function.

Furthermore, the Examiner's Answer clearly addresses this assertion by appellant that assigning structure and function based upon homologous nucleotide sequences under 35 USC 112, first paragraph, enablement and written description, as each of the MAGEs relied upon by appellant to support the claimed genus differ in their structure at both the amino acid and nucleic acid levels as well as differ in their expression and putative function as tumor antigen precursor proteins.

For example, see the review of the information disclosed in the specification as filed and De Plaen et al. (Immunogenetics 40: 360-369, 1994) on pages 6-9 as well as the Response to Appellant's Arguments in the Examiner's Answer.

Also, the skilled artisan can look at the diversity of structure, expression and function of the MAGEs encompassed by the claimed invention and disclosed in the specification as filed to determine that homologous nucleotide sequences do not result in proteins that have the an identifiable structure that is correlated to its expression and function as a MAGE TRAP protein in contradistinction to appellant's assertions.

While appellant provided a listing of references which evidence that MAGE molecules do stimulate T cells, these references appear to support stimulation of T cells with only certain MAGEs (e.g. MAGE-1, MAGE-3) and not the genus of MAGE tumor antigen precursors encompassed the claimed invention, nor asserted by appellant.

Further, appellant has not provided sufficient nexus between the specific MAGE peptides disclosed in these post-filing date references Vantomme et al. (J. Immunother 27: 124-135, 2004), Zhang et al. (Journal of Immunology 171: 219-225, 2003) and Atanackovic et al. (Journal of Immunology 172: 3289-3296, 2004) with the instant specification as filed.

The instant specification does not disclose MAGE-3 tumor rejection peptides, much less the ones described by appellant's newly submitted references.

Other than relying upon post-filing date references identifying MAGE 3 peptides not disclosed in the specification as filed,

appellant has not provided sufficient evidence to support the identification of MAGE-derived peptides that may be important in stimulating immune responses from the others MAGEs disclosed in the specification as filed and relied upon by appellant to support the generic claims,

nor has appellant's specification as filed provided for the association between a particular MAGE, a particular tumor rejection antigen peptide derived from that MAGE and the particular MHC HLA association with that MAGE or tumor rejection antigen peptide,

other than SEQ ID NO: 26 for MAGE-1 (SEQ ID NO: 8).

Further with respect to "vaccines",

it is noted that Vantomme et al. (J. Immunother 27: 124-135, 2004, cited by appellant concludes that:

" In the cancer immunotherapy field, a correlation between immune responses induced by vaccination and the clinical response has been difficult to establish. Although some correlation has been reported by some groups, there is no consensus in the scientific community of the correlates of protection or the appropriate immune readout for monitoring cancer vaccine clinical trials."

See Conclusions and Perspectives on page 133 of Vantomme et al.

Similarly, Atanackovic et al. (Journal of Immunology 172: 3289-3296, 2004) conclude by stating:

"The data presented in this work lay the grounds for the design of vaccine constructs and immunization protocols to define conditions for maximal immunogenicity and answer the most important question in tumor immunology: can immunization affect the course of human cancer"

See the last paragraph on page 3295 of Atanackovic et al.

In addition to the lack of nexus between these post-filing date references and the instant specification concerning the identification of MAGE-3 peptides that may stimulate immune responses,

these references support the position that "cancer vaccines" raise additional levels of consideration under 35USC 112, first paragraph, with respect to satisfying the characteristics of "vaccine", as currently recited in claims 189-191.

While appellant relies upon U.S. Patent No. 5,405,940 to show that regions of various MAGE coding sequences are comparable to SEQ ID NO: 26 and that peptides do function as TRAs (i.e. tumor rejection antigens),

Again appellant has not provided neither the written description nor the enablement of the appropriate TRAs associated with either each or a representative number of species to support the genus of MAGE precursors currently claimed.

On column 7, paragraph 2 of U.S. Patent No. 5,405,940, the following is noted:
"The MAGE-1 derived nonapeptide appears to HLA-A1 specific. Although the MAGE-2, MAGE-3 and MAGE-4 genes have all been observed to be expressed in HLA-A1 cells of tumors, the peptides corresponding to MAGE-1 have not been shown to elicit the same specific CTL response; however it may be expected that these nonapeptides do provoke response by different CTL when bound to an appropriate HLA molecule".

Therefore, appellant has provided additional evidence to support the position that there is not a correlation between structure and function based upon homology with SEQ ID NO: 8 as each MAGE is distinct on its primary amino acid structure, its encoding nucleic acid, its expression and its ability to stimulate appropriate anti-tumor CTL responses with appropriate MHC HLA as well as whether the MAGE is indeed associated with cancer that would satisfy the MAGE TRAP characteristics (i) –(iv).

Here in this case, it is clear that appropriate MAGE tumor rejection antigen peptide and its corresponding MHC / HLA molecule are distinct for each MAGE and that each MAGE is mutually exclusive in its structural and functional properties as a putative tumor rejection antigen precursor protein.

Isolation and characterization of MAGE tumor rejection antigen precursor proteins that satisfy the *MAGE TRAP characteristics (i)-(iv)* rely upon more than mere reliance upon whether a myriad of nucleic acids will hybridize with SEQ ID NO: 8 and that among said myriad of nucleic acids, coding regions are determined and that these putative coding regions encode a MAGE tumor rejection antigen precursor protein that satisfy said *MAGE TRAP characteristics (i)-(iv).*

As appellant has noted there is not a "one on one" correspondence of HLA and TRAP. While appellant assert that alone needs is a blood sample to derive the relevant CTL, the Examples in the specification as filed appear to rely upon the availability of CTLs to test the ability of a MAGE to stimulate a T cell.

The specification as filed did not provide for the appropriate CTLs for all of the MAGEs disclosed in the specification as filed and encompassed by the claimed invention.

Further, the evidence of record does not provide for certain MAGEs such as MAGE 5, 7, 8, 9, 10 and 11 to provide for TRAs peptides in order to stimulate an immune response or a vaccine response for tumor therapy.

As pointed out above, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 (EADPTGHSY) which stimulates proliferation of CTLs and which is specific for MAGE-1 and MHC HLA –A1.

As noted previously and according to the Listing of TRAPS submitted with the Brief, it appears that SEQ ID NO: 26 (EADPTGHSY) of MAGE-1 can complex with HLA B35.

However, the specification as-filed does not provide a written description for this observation that MAGE-1 derived peptides can complex with HLA molecules other than HLA-A1.

As disclosed on page 55, paragraph 1 of the instant specification, the sequences code for "tumor rejection antigen precursors" (TRAPS) which, in turn, are processed into tumor rejection antigens (TRAs). Isolated forms of both of these categories are described herein, including specific examples of each. Perhaps their most noteworthy aspect is as vaccines for treating various cancerous conditions. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. The examples show that when various TRAs are administered to cells, a CTL response is mounted and presenting cells are deleted. This is behavior characteristic of vaccines, and hence TRAPS, which are processed into TRAs, and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions, as vaccines.

As disclosed on page 30, paragraph 2 of the instant specification, in isolating the pertinent nucleic acid sequence for a tumor rejection antigen precursor, the techniques developed by appellant showed that a recipient cell is needed which fulfills two criteria:

(i) the recipient cell must not express the TRAP of interest under normal conditions, and

(ii) it must express the relevant class I HLA molecule.

Therefore, it appears that either it was necessary to have the appropriate CTLs readily available and know what was the relevant class I HLA molecule associated with each MAGE TRAP protein OR determine said characteristics by trial and error in order to determine whether a MAGE TRAP protein satisfied the four criteria *(i)-(iv) for a MAGE TRAP.*

Consistent with the specification as filed and appellant's arguments, it is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.**).

The specification as-filed does not appear to provide for a CTL to test whether MAGE-1 TRAP protein or a MAGE TRAP protein comprising SEQ ID NO: 26 can complex with HLA B35, as relied upon by appellant in providing the listing of TRAP immunogenic peptides.

While appellant asserts that all one needs is a blood sample and that the relevant CTLs are developed therefrom, it would appear that this is consistent with the position that appellant has provided a plan to test all possible nucleic acid sequences that hybridize to SEQ ID NO: 8 and then subject said nucleic acid candidates to various assays and analyses to determine whether these nucleic acid candidates encode a putative MAGE tumor rejection antigen precursor can satisfy the *MAGE TRAP characteristics (i)-(iv),* indicating both a lack of possession and enablement at the time the invention was made to support the broad genus, as currently recited.

In contrast to the Listing of TRAPS or examples provided in the Brief or in the Reply Brief, the disclosure of a single peptide obtained from MAGE-1 and its association with HLA-A1 in the specification as-filed does not provide for a sufficient number of species of TRAs or their association with specific MHC molecules to satisfy the genus of MAGE TRAP proteins, encompassed by the claims.

The specification as-filed does not provide for the complete cDNA nor the amino acid sequences as well as isolation for each of the MAGE 1-11 disclosed in the specification as filed.

The skilled artisan would not have sufficient information to determine whether the incomplete putative MAGE genomic sequences disclosed in the specification as filed provided the appropriate amino acid sequences that would serve as appropriate tumor rejection antigen peptides and what MHC HLA Class I molecules would be associated with said peptides.

Given the absence of providing sufficient information (e.g. cDNA or amino acid sequence) concerning MAGE TRAP proteins, the specification as-filed did not provide a sufficient correlation between a particular MAGE TRAP protein and its associated tumor rejection antigens (TRAs) which complex to different MHC molecules to form targets for CTLs.

With respect to stringent conditions, it is simply noted that the claims do not recite the phrase "stringent conditions".

However, one of the MAGE TRAP characteristics is
(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions.

The conditions for hybridization are designed with controlling both salt conditions and temperature to control the rate formation.

The instant claims do not recite temperature conditions that would necessarily lead to high stringency conditions which are used to detect identical or very highly conserved genomic sequences complementary to the probe sequence, as apparently asserted by appellant.

For example, see the following from pages 36-38, particularly page 38, and pages 46-49 of the Examiner's Answer.

As noted above, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Given that the claims encompass nucleic acids that hybridize to SEQ ID NO: 8 and Given that "variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2 or Kirkin et al.), appellant was not in possession of a genus of MAGE TRAP proteins comprising SEQ ID NO: 26 wherein the MAGE TRAP protein relies upon nucleic acids that hybridize to SEQ ID NO: 8. Given the hybridization language encompassed by the claims, the claimed MAGE TRAP proteins comprise variations in amino acid sequences. Therefore, there is insufficient evidence that appellant was in possession of a genus of MAGE TRAP proteins comprising SEQ ID NO: 26 that would provide SEQ ID NO: 26 itself and, more importantly, provide SEQ ID NO: 26 that is recognized by an appropriate CTL.

Written description requires for the functional characteristics *(see TRAP characteristics)* of a MAGE TRAP protein to be coupled with a disclosed correlation to a structure (i.e. nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8). Sufficient disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described rather than merely describing the claimed subject matter in functional terms as a MAGE TRAP protein which are encoded by nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 wherein the isolated TRAP comprises SEQ ID NO: 26.

Appellant notes that if MAGE-7 does not possess the relevant functional attributes of the claims, then it is not being claimed.

While it is appreciated that appellant acknowledges that MAGE-7 does not meet the claimed limitations,

appellant has asserted that the disclosed Examples provide 11 species that satisfy the claim limitations (See Brief on Appeal).

Also, in the Reply Brief (see page 4, paragraph 1), appellant relies upon MAGE-7 presenting a coding region.

While appellant submits that Ding et al. (Biochem. Biophys. Res. Comm. 202: , 1994), shows further molecules which hybridize to SEQ IDNO: 8 and function as TRAPS, it is noted that Ding et al. present the full length sequence of 5 expressed genes including two previously unreported MAGE genes and discuss their potential to encode novel tumor antigens (see Introduction on pages 549-550). In addition to the two previously unreported MAGE genes, the specification as filed did not provide for written description nor enablement of MAGE-12 as well. Ding et al. also describes amino acid differences in the HLA-A1 anchor binding motif which would presumably alter the T cell receptor recognition of these and peptides and could change the affinity of the peptides for the HLA-A1 binding pocket (see page 552, paragraph 2).

Therefore, Ding et al. provided full length sequences rather than relying upon a number of partial sequences, relied upon by a number of appellant's disclosed MAGE species.

Also, Ding et al. is consistent with the rejections of record in that amino acid differences in HLA binding motif will alter T cell recognition.

Therefore, reliance upon hybridizing structural language lends itself to multiple amino acid changes and presumably different, if any, recognition by CTLs, as encompassed by the *MAGE TRAP characteristics (i)-(iv).*

Appellant's arguments concerning written description, including distinguishing the decisions in on Federal Circuit decisions and Written Description Guidelines and Examples, from the rejection of record is acknowledged.

In contrast to appellant's assertions that the examiner has not addressed appellant's arguments, the examiner maintains that the record is replete with reasons and evidence to support the written description rejection under 35 USC 112, first paragraph, of record.
See the Examiner's Answer for a more complete analysis.

Example 9 of the Written Description Guidelines does not control the facts of this case.

While Example 9 does note that the disclosure of a single cDNA which encodes a protein of known structure is adequate written description for an isolated nucleic that specifically hybridizes under highly stringent conditions to the complement of the cDNA sequence,

However, the claimed genus in the instant application still encompasses an enormous number of species with potentially widely diverse properties and describes them structurally simply by hybridization language.

The record, including the Examiner's Answer, is clear that each of the disclosed putative MAGEs disclosed in the specification as filed does not satisfy the MAGE TRAP characteristics (iv)-(iv), in contrast to the assertions by appellant.

It is noted that each case is decided on its own facts and the facts of record support the rejections under 35 USC 112, first paragraph, written description and enablement, given the generic claim language and the absence of a correlation between structure and function of proteins encoded by nucleic acids that hybridize to SEQ ID NO: 8 and their ability to satisfy the *characteristics (i)-(iv) of a MAGE tumor rejection antigen precursor protein.*

Again, the rejections of record are consistent with appellant's reliance on defining the *characteristics of MAGE TRAPs* and protocols for securing said MAGE TRAPs and the evidence of record.

In contrast to appellant's assertions that the issue relating to vaccines and low immunogenicity and low immune response was raised for the first time in the Examiner's Answer, the issue of vaccines and low immunogenicity was raised in the Office Action, mailed 3/2/04.

The addition of the Dictionary Definition of "vaccine" in the Examiner's Answer was for the convenience of the Board in discerning the meaning of this term in the claim.

During patent examination, the pending claims are given their broadest reasonable interpretation consistent with the specification, which in turn, is consistent with the interpretation that those skilled in the art would reach. See MPEP 2111.

See the comments above in I. Grouping of Claims.

Also, for example, see the following from the Examiner's Answer.

C) Examiner Submits That The Rejection of Claims 189-191 for Failing to Satisfy the Written Description Requirement of 35 USC 112, first paragraph Should Stand or Fall Together on pages 38-41 of the Examiner's Answer.

C) Examiner Submits That The Rejection of Claims 189-191 for Failing to Satisfy the Enablement Requirement of 35 USC 112, first paragraph Should Stand or Fall Together on pages 52-55 of the Examiner's Answer.

While appellant asserts that the claims are product claims and no "use claims" are presented, Appellant has clearly indicated that the claims are drawn to MAGE tumor antigen precursor proteins that are defined in terms of the *MAGE TRAP protein characteristics (i)-(iv),*
which include isolated proteins
(versus reliance upon partial genomic nucleic sequences),
which are characteristic of cancer cells
(versus the lack of or weak expression of MAGE –5, -8, –9, -10 and –11 in cancer tissues and no transcription of MAGE-7) and
which are processed, intracellularly, into tumor rejection antigens that form targets for CTLs
(which the specification provides very limited information and appellant relies upon observations in post-filing date MAGE-3-related references) and
wherein the claims recite "vaccine", which does encompass intended use
(and which insufficient objective evidence has been provided to support the genus claims).

The recitation of "vaccine" does raise issues under 35 USC 112, first paragraph, regardless of whether the claims are product claims or use claims.

In addition, appellant has been clear that the claimed MAGE TRAP proteins have the *MAGE TRAP characteristics (i)-(iv)* and, in turn, the claims have been read in the context of such *characteristics.*

With respect to appellant's assertions that reliance upon the key cases standing for the Written Description were inappropriate and that the Written Description Guidelines, including Example 7, do not support the rejection of record, the following is noted.

In contrast to appellant's assertions both the courts and Written Description Guidelines have been clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In Enzo Biochem Inc v Gen-Probe Inc 285 F3d 1013 (Fed Cir 2002), the court broadened what is sufficient description, in that not all function descriptions of genetic material would fail to meet the written description requirement, particularly not when functional characteristics are coupled with a known or disclosed correlation between function and structure, yet the materials in question comprised the same species.

Extending this finding is the recent decision in In re Wallach, 71 USPQ2d 1939 (CA FC 2004), where claims to a nucleic acid were rejected for lack of adequate written description, where the inventors disclosed a partial protein structure and characterization of the protein, yet such description was insufficient for claims directed to the claimed nucleic acid

In the Wallach case, the Federal Circuit found that because the inventors did not know the complete amino acid sequence of the protein at the time of filing their patent application, they did not possess any of the DNA sequences encoding the isolated protein.

The court ruled that although the written description requirement can in some cases be satisfied by functional description, this is only sufficient if there is a known structure-function relationship. In this Wallach case, applicant did not provide evidence that a known or disclose correlation between the combination of a partial structure of a protein and the structure of the DNA encoding the protein on the other.

These later written description court cases are consistent with earlier court decisions.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed tumor antigen precursor and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

While the instant specification discloses 11 closely related MAGE genes that have been identified by probing cosmid libraries with a MAGE-1 sequence, the application as-filed did not provide a sufficient disclosure of sufficiently, detailed, relevant identifying characteristics which provide evidence that appellant was in possession of the claimed invention of MAGE TRAP proteins that satisfy the *TRAP characteristics*. The disclosure must show that the inventor has invented each feature that is included in a claim limitation. Appellant must convey with reasonable clarity to those skilled in the art that as of the filing date sought, he or she was in possession of the invention. One does need to be able to describe the invention with particularity.

Adequate written description require a precise definition, such as structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. Appellant has not satisfied the written description of the MAGE TRAP genus of polypeptides in the absence of a disclosed correlation to a structure and possessed a sufficient number of species that satisfy the *MAGE TRAP protein characteristics* asserted by appellant.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 itself, much less, nucleic acids hybridizing to SEQ ID NO: 8, and any or all of the *MAGE TRAP properties* outlined in the Examiner's Answer.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 and MAGE TRAP protein expression itself or expression of a MAGE TRAP protein.

For example, the disclosed MAGE-7 has not been found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained at least up to the 1994 publication date of **De Plaen et al.** (see page 364, column 2, first full paragraph of **De Plaen et al.)**.

Again, as indicated above, the specification as-filed does not provide for the complete encoding cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein itself for each of the 11 species of MAGE 1-11 disclosed in the specification as filed.

Importantly, it is noted that claims are not even limited to SEQ ID NO: 8 itself, but rather encompass nucleic acid molecules that hybridize to SEQ ID NO: 8, thereby a greater diversity of nucleic acid sequences and, in turn, a greater diversity of amino acid sequences encoding a MAGE TRAP protein are encompassed by the claims.

As appellant acknowledges, the hybridization language provides for a diversity of nucleic acids and, in turn, a diversity of amino acids and MAGE TRAP proteins. Such hybridization language encompasses distinct MAGE TRAP nucleic acids and, in turn, putative MAGE TRAP proteins, each of which differ with respect to the *MAGE TRAP characteristics* relied upon by appellant.

The claimed hybridization conditions to a referenced nucleic acid does not result in MAGE TRAP proteins that have all of the identifiable properties or *TRAP characteristics* of MAGE-1 or a MAGE TRAP protein, as evidenced by the instant record.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, the specification as-filed does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species, not all of which meet the critical *characteristics of MAGE TRAPs* asserted in the Brief.

Written description requires for the functional characteristics *(see TRAP characteristics)* of a MAGE TRAP protein to be coupled with a disclosed correlation to a structure (i.e. nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8). Sufficient disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described rather than merely describing the claimed subject matter in functional terms as a MAGE TRAP protein which are encoded by nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8.

Akin, to the recent CAFC decision in Wallach, the skilled artisan would not rely upon the partial encoding genomic nucleic acid sequences of the disclosed MAGEs to support appellant's assertions that the specification as filed provided 11 MAGE protein species that satisfy the structural as well as the functional requirements of MAGE tumor rejection antigen precursor proteins, broadly claimed.

Akin to the continual holdings of the court decisions addressing written description, adequate written description require a precise definition, such as structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. Appellant has not satisfied the written description of the MAGE TRAP genus of polypeptides in the absence of a disclosed correlation to a structure and possessed a sufficient number of species that satisfy the *MAGE TRAP protein characteristics* asserted by appellant.

Appellant's reliance upon hybridizing language in the absence of disclosed correlation to structures that satisfy the *MAGE characteristics* as well as upon the disclosed MAGEs does not comport with the evidence of record, including the limited structural and functional characterization of said MAGE species disclosed in the specification as filed as well as by De Plaen et al., which provides a more complete analysis of MAGE proteins

It is acknowledged that correction of the sequencing error in SEQ ID NOS 7 and 8 was permitted.

While appellant relies upon homologous structure and function, the examiner simply pointed out that even appellant was not cognizant of the correct sequence for the base sequence of MAGE-1.

Given a wrong reference sequence the ability to encode a MAGE tumor rejection antigen precursor protein and in turn, its use in generating the desired immune responses would be compromised.

With respect to the written description of SEQ ID NOS 7 and 8, it appears that these sequences can encode for an entire MAGE-1 tumor antigen precursor protein, while a number of the other putative MAGE sequences disclosed in the application as filed are incomplete genomic sequences and do not satisfy the *MAGE TRAP characteristics (i)-(iv)* assigned to the claimed products.

A discussion concerning the reliance upon post-filing date references has been set forth on pages 25-26 of the Examiner's Answer. See **(11) Response to Argument.**

It is acknowledged that enablement is determined as of the effective filing date of the application,

If an inventor claims what was specifically desired but difficult to obtain at the time the application was filed, the claims are enabled only if the application discloses how to make and use it.

While MAGE tumor rejection antigen precursor proteins were desired as of the filing date, isolating and determining whether hybridizing nucleic acids encode MAGE tumor rejection antigen precursor proteins that satisfy the *MAGE TRAP characteristics (i)-(iv)* were difficult to ascertain at the time the invention was made;

the instant application has provided for partial genomic sequences (versus either nucleic acids or amino acid sequences that encode entire MAGE precursor proteins);

the instant specification has provided insufficient nexus between structure and the *MAGE TRAP characteristics (iv)-(iv); and*

the instant specification provided limited expression and functional information on each of the disclosed putative MAGEs.

Appellant has not addressed the deficiencies of their assertion that each of the disclosed MAGEs satisfy the MAGE TRAP criteria (i)-(iv).

While appellant continues to rely upon this provision of the a precise definition of what is claimed, it appears that appellant continues to simply assert that nucleic acids that hybridize to SEQ ID NO: 8 are MAGE TRAPS, rather a "mere wish or plan for obtaining the claimed invention.

The Office is not in position to test and is relying, in part, for the evidentiary record to for analysis

The evidence of record clearly indicate that not all of the disclosed putative MAGE species satisfy the *MAGE TRAP characteristics (iv)-(iv)* and that each MAGE was structurally and functionally distinct and exclusive from one another.

The rejections of record used post-filing date references, including the co-inventors own work to support such rejections under 35 USC 112, first paragraph.

For example, in order to ascertain appellant's assertions that all of the disclosed MAGEs satisfy the *criteria for MAGE TRAPs*, the examiner focused analysis in the Examiner's Answer on the actual evidence as to the structure, expression and functional properties of the disclosed MAGEs, as evidenced by appellant in the specification as filed as well as in appellant's co-authored reference by the De Plaen et al.

As the court noted in Chiron Corp. v. Genentech Inc. (70 USPQ2d 1321, 1328 (CAFC 2004); " We do not read Hogan as allowing an inventor to claim what was specifically desired but difficult to obtain at the time the application as filed, unless the patent discloses how to make and use it".

The instant case is not one in which the rejection is based upon enabling an unknown, future technology by relying upon post-filing date references.

Rather the post-filing date references noted herein have been employed to provide evidence, including appellant's own co-authored references, that identifying and characterizing human tumor precursor rejection antigen proteins at the time the invention was made was difficult in terms of possession in terms of written description and in terms of how to make and use in terms of enablement.

The post-filing date references provide for permissible knowledge concerning appellant's assertions of satisfying the requirements under 35USC 112, first paragraph, at the time of filing the instant application.

The function of the written description requirement is to ensure that the invention had possession, as of the filing date of the application relied upon, of the subject matter claimed.

In this case, appellant did not have possession of a sufficient number of species that satisfy the *MAGE TRAP characteristics (i) – (iv),* nor provide for a correlation between structure and function of said *MAGE TRAP characteristics.*

Applications satisfy the enablement requirement of one skilled in the art after reading the instant disclosure could practice the full scope of the claimed invention without undue experimentation.

In this case, the record is clear that appellant's reliance on the disclosed MAGE species do not satisfy the *MAGE TRAP characteristics (i)-(iv)* and that it would have taken undue experimentation to practice the full scope of the claimed invention.

In fact, it appears that appellant reliance on post-filing date references to support the isolation and characterization of putative MAGE-3 tumor rejection antigens appears to be supplementing an insufficient disclosure in a prior dated application to render it enabling.

IV. RESPONSE TO THE EXAMINER'S ARGUMENT THAT CLAIMS 184, 187 AND 190 DO NOT SATISFY THE WRITTEN DESCRIPTION REQUIREMENT

Appellant submits that these claims require that the claimed molecule include the amino acid sequence of SEQ ID NO: 26 and that SEQ ID NO: 26 is a tumor rejection antigen.

See pages 32-35 of the Examiner's Answer for a more complete analysis and rebuttal to appellant's arguments.

Appellant states that the fact that the peptide can form a complex with another HLA molecule is not seen as relevant, since the claims do not require a specific HLA molecule as a partner.

Appellant notes that assuming arguendo that no CTLS were available, surely it is within the skill of the artisan to make a nonamer, admix it with a cell presenting HLA-A1 molecules, and then stimulate the production of the CTLs. Once these are in hand, the CTLs can identify relevant other complexes, those formed by action of TRAPs containing SEQ ID NO: 26

Again, there is a lack of correlation between structure and function between hybridizing nucleic acids to genomic DNA and in turn whether such hybridizing sequences comprising SEQ IUD NO: 26 would be properly present the appropriate tumor rejection antigen peptide defined by SEQ IDNO: 26

Note the following reiterated from above.

While appellant relies upon U.S. Patent No. 5,405,940 to show that regions of various MAGE coding sequences are comparable to SEQ ID NO: 26 and that peptides do function as TRAs (i.e. tumor rejection antigens),

Again appellant has not provided neither the written description nor the enablement of the appropriate TRAs associated with either each or a representative number of species to support the genus of MAGE precursors currently claimed.

On column 7, paragraph 2 of U.S. Patent No. 5,405,940, the following is noted:
"The MAGE-1 derived nonapeptide appears to HLA-A1 specific. Although the MAGE-2, MAGE-3 and MAGE-4 genes have all been observed to be expressed in HLA-A1 cells of tumors, the peptides corresponding to MAGE-1 have not been shown to elicit the same specific CTL response; however it may be expected that these nonapeptides do provoke response by different CTL when bound to an appropriate HLA molecule".

Therefore, appellant has provided additional evidence to support the position that there is not a correlation between structure and function based upon homology with SEQ ID NO: 8 as each MAGE is distinct on its primary amino acid structure, its encoding nucleic acid, its expression and its ability to stimulate appropriate anti-tumor CTL responses with appropriate MHC HLA as well as whether the MAGE is indeed associated with cancer that would satisfy the MAGE TRAP characteristics (i) –(iv).

Here in this case, it is clear that appropriate MAGE tumor rejection antigen peptide and its corresponding MHC / HLA molecule are distinct for each MAGE and that each MAGE is mutually exclusive in its structural and functional properties as a putative tumor rejection antigen precursor protein.

Isolation and characterization of MAGE tumor rejection antigen precursor proteins that satisfy the *MAGE TRAP characteristics (i)-(iv)* rely upon more than mere reliance upon whether the myriad of nucleic acids that hybridize with SEQ ID NO: 8 and that among said myriad of nucleic acids, coding regions are determined and that these putative coding regions encode a MAGE tumor rejection antigen precursor protein that satisfy said *MAGE TRAP characteristics (i)-(iv).*

V. THE REJECTION OF NEW GROUP CONTAINING CLAIMS 189-191.

Appellant's arguments and the examiner's rebuttal are set forth above in the **I. Grouping of Claims.**

VI. THE EXAMINER'S POSITION WITH RESPECT TO THE ENABLEMENT OF CLAIMS 183, 185, 186, 188, 189 AND 190 (VERSUS 198)

While appellant wonders "how can one respond to an argument if no argument is made?, The examiner maintains that the Examiner's Answer is replete with a detailed analysis concerning the enablement of the claimed invention.

VII. THE NEW REJECTION OF CLAIMS 189-191 AS LACKING ENABLEMENT

While MAGE-1 appears to satisfy the criteria for a vaccine, the Examiner's Answer as well as this Supplemental Examiner's Answer addresses the issue of "vaccine" as it reads on the breadth of the claimed MAGE tumor rejection antigen precursors, including an analysis of the disclosed putative MAGE species that appellant has asserted satisfy the MAGE TRAP characteristics, including the recitation of "vaccine" in claims 189-191.

VIII. Conclusions

As pointed out in the Examiner's Answer and in contrast to appellant's assertions,

the instant specification does not provide for 11 species that meet the key *characteristics of MAGE TRAPs*, including:

(i) they are proteins that are encoded by naturally occurring, non-mutagenized gene;

(ii) they are characteristic of cancer cells and are not expressed by normal cells (with the exception of testes cells;

(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions; and

(iv) they are processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs.

In contrast to appellant's assertions, the Examiner's Answer provides a detailed analysis that contradicts appellant's assertions that the 11 species disclosed in the specification as filed provide for representative species of the claimed genus of MAGE tumor antigen precursor proteins with these *MAGE TRAP characteristics (i) – (iv).*

Rather than simply relying upon the insufficiency of MAGE-7 alone as asserted by appellant, the Examiner's Answer carefully reviews the inconsistencies between the *MAGE TRAP key characteristics* as noted by appellant and the evidence that would support such a conclusion that the generic claims are subject to rejections under 35USC 112, first paragraph, written description and enablement.

For the reasons set forth in the Examiner's Answer and addressed herein in response to appellant's Reply Brief, it is believed that the rejections should be sustained.

Respectively submitted,

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